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DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Drugs Affecting Psychotic Behavior and the Function of the Mesodiencephalic Activating System

FRANCO RINALDI, M.D., and HAROLD E. HIMWICH, M.D.
Galesburg, Illinois

In the last ten years neurophysiological researches have led to the recognition of the functional importance of a central core of gray matter extending from the upper spinal cord to the thalamus.[20] The bulbar, pontine and mesencephalic parts of this gray matter complex are called the brain stem reticular formation (BSRF). It has been shown that the bulbar portion of the reticular formation exerts inhibitory influences on spinal motor activity,[33] while the portion above the bulb possesses a facilitatory control over spinal cord activity.[26] Beside these centrifugal actions, it has been demonstrated that the BSRF influences the function of the cephalad portion of the nervous system, namely the cerebral cortex. For instance, the integrity of the BSRF has proved to be a factor for the maintenance of wakefulness.[18,19] Furthermore, the BSRF has widespread control over the electrical activity of the cerebral cortex. The diffuse electrocorticographic changes following peripheral stimulus, changes that are known as the activating, arousal or alerting responses[25] are mediated through the BSRF.[21] The corticipetal influence of the BSRF is probably extended through those thalamic mechanisms that have a diffuse projection over the cerebral cortex,[14] different therefore from the specific relay system of the thalamus and consequently called the thalamic diffuse projection system (TDPS). We may consider, as far as the diffuse effect on the electrical activity of the cerebral cortex is concerned, both the BSRF and TDPS as a unitary system hereafter called the mesodiencephalic activating system (MDAS). Through the MDAS, an unspecific indirect multineuronal pathway, afferent impulses, carried by collaterals of the specific lemniscal sensory pathway, can reach the cerebral cortex. It is mainly by means of this mechanism that the alerting responses are produced. The functional meaning of the alerting response is however little understood. Our knowledge is limited to a description of electrical phenomena. Following a peripheral stimulus two separate effects are produced: one localized to the specific projection area of the cortex, the so-called evoked potential, the other a diffuse general change in the patterns of cortical activity. The EEG record reveals the elimination of all slow high voltage activity such as the one observed during sleep, as well as the appearance of low voltage fast activity. The latter effect is the activating, arousal or alerting response. A claim has been made for a relationship between this electrographic reaction and the production and maintenance of behavioral alertness or wakefulness in accordance with the previously mentioned activation of the MDAS in the maintenance of the wakeful state.[20] More generally it is thought that it is a function of the MDAS

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to support in a diffuse manner a background of activity in the cortex. This basal activity of the cortex, or cortical tonus, is probably of importance in general cortical physiology and specifically in the regulation of the level of consciousness, of awareness and mental activity. Beside these general concepts of the MDAS we do not know whether it participates in mental functions nor whether it plays any part in abnormal mental states.

In a recent experimental study[27,28] observations were made on the physiology and the pharmacology of the MDAS revealing that certain drugs have specific actions on the MDAS. In the studies it was demonstrated that atropine has the property of paralyzing selectively the function of the MDAS. Atropine not only prevents the electroencephalographic alerting reaction following peripheral stimulation, but also inhibits the reaction following a direct electrical stimulation of the MDAS at the mesencephalic level. Cholinergic drugs such as acetylcholine (ACh) and di - isopropyl - fluorophosphate (DFP) stimulate the MDAS and therefore exert effects opposite to those of atropine. It has been also shown that this action of cholinergic drugs is not a general diffuse one, but is specific for the MDAS. This fact and the opposite signs of the action of the two groups of drugs, the cholinergic are stimulants of the MDAS while the anticholinergic ones are inhibitors of the MDAS, lead to the conclusion that a cholinergic mechanism is involved in the function of that system.[28] Following the lead offered by these observations, we studied the effect of a number of drugs on the MDAS to see whether any correlation could be found between changes of the functional condition of the MDAS and the neurological and psychiatric effects of these drugs. The results obtained with a group of drugs that have been beneficially employed in the treatment of the Parkinson syndrome were reported elsewhere.[29] It was found that the effectiveness of drugs in the treatment of Parkinson's syndrome was directly proportional to the degree of inhibition they exerted on the MDAS, thus mimicking the central action of atropine. This supports the hypothesis of an involvement of the BSRF in the production of the symptoms of Parkinson's disease. Such information might also turn out to be useful to elucidate the involvement of the MDAS in mental function especially if comparisons were made between the experimentally proved action of drugs on the MDAS and their effects on the behavior of normal individuals and of psychiatric patients. In the present paper we report the effects on the MDAS of a group of drugs affecting psychiatric behavior: Reserpine (Serpasil of the Ciba Company); Chlorpromazine (10-gamma-Dimethylamino-propyl-2 Chlorophenothiazine Hydrochloride; Thorazine of the Smith, Kline and French Laboratories); Pipradrol (alpha-2-Piperidyl Benzohydrol Hydrochloride; Meratran of the Wm. S. Merrell Company); Frenquel (alpha-4-Piperidyl Benzohydrochloride, MER-17 of the Wm. S. Merrell Company). A correlation will be attempted between these results and the clinical effects produced by these drugs and by others, like atropine and DFP, that are specifically active on the MDAS.

Methods

The experimental technique employed is the same one described in the precedent studies.[27] All experiments were performed in adult albino rabbits curarized and maintained by artificial respiration. The electrical activity of the brain was recorded by means of electrodes placed on the motor cortex, in the head of the caudate nucleus, on the limbic cortex and in the medial thalamus. Another electrode (bipolar of stainless steel) was placed so that its tip was located in the midbrain reticular substance at the level of the anterior quadrigeminal body. This electrode was used for direct stimulation of that formation. In all brains used in this study, the intracerebral location of the electrodes was checked by means of serial sections of formalin-fixed, paraffin-embedded whole brain. The sections were stained with a combined technique for myelin sheaths and nerve cells.[16] Brain electrical activity was recorded with an eight channel ink-writing electroencephalograph. To stimulate the midbrain reticular substance direct current pulses of a frequency of 300/sec and 2 milliseconds in duration were employed. The voltage of stimulation (1-8 volts) and the duration of application of the stimulus (0.5-3

seconds) were so adjusted that stimuli were always slightly above threshold values. These parameters had been found optimal for the production of the alerting reaction.

Peripheral stimulations were also used: hand clapping as auditory, touching the hair on a leg as tactile, and twisting of digital joints as painful stimulation.

The experimental drugs were given intravenously in varying amounts which will be specified below.

Criteria Followed in the Evaluation of the Effect of Drugs on the Mesodiencephalic Activating System.

The brain electrical activity of the rabbit, maintained at a constant level of curarization and in carefully regulated conditions of artificial respiration shows two well defined patterns (Figure 1). 1. The first pattern is observed when the animal is left undisturbed; we will call it the resting or sleep pattern. It is characterized by high voltage (100-300 microvolts) slow (1-3 and 4-6 c/s) waves and spindles of 14 c/s waves. The spindles are prominent in the motor cortex. (For detailed regional differences of this pattern see Rinaldi and Himwich[27]). This type of activity continues unbroken until some accidentally or purposefully induced stimulus (auditory, tactile, painful, etc.) disrupts it and brings forth instead the second pattern. 2. The latter pattern is characterized by (a) the disappearance of all slow waves and of spindles; (b) the appearance of a very regular 4-6 c/s rhythm of medium amplitude in the thalamus; (c) the presence in the caudate and in the cortex of fast low voltage activity and, chiefly in the latter, of a rhythm similar to the thalamic one. We will call this picture the alert pattern. The onset of the alert pattern is always abrupt and the duration of it varies with the type and the intensity of the stimulus. Pain is the most efficacious peripheral stimulus, while sound is the least efficacious.

The direct electrical stimulation of the midbrain reticular formation has the same effect of inducing an alert EEG picture. This stimulation produces electrographic alertness of the longest duration. Moreover, it has the advantage of making possible (a) the measurement of variations of threshold (b) the measurement of variations in duration of the effect using a fixed above-threshold intensity.

In accordance with experience gained in the studies with cholinergic drugs, specific stimulants of the MDAS, and with anticholingeric ones, specific inhibitors of the MDAS, we established a series of criteria that permitted not only the evaluation of the type of action exerted by drugs on the MDAS, but also the empirical evaluation of the degree to which the action was exerted.

In the course of a depressant action, we distinguished three progressive stages of depression. First stage of depression; ab-

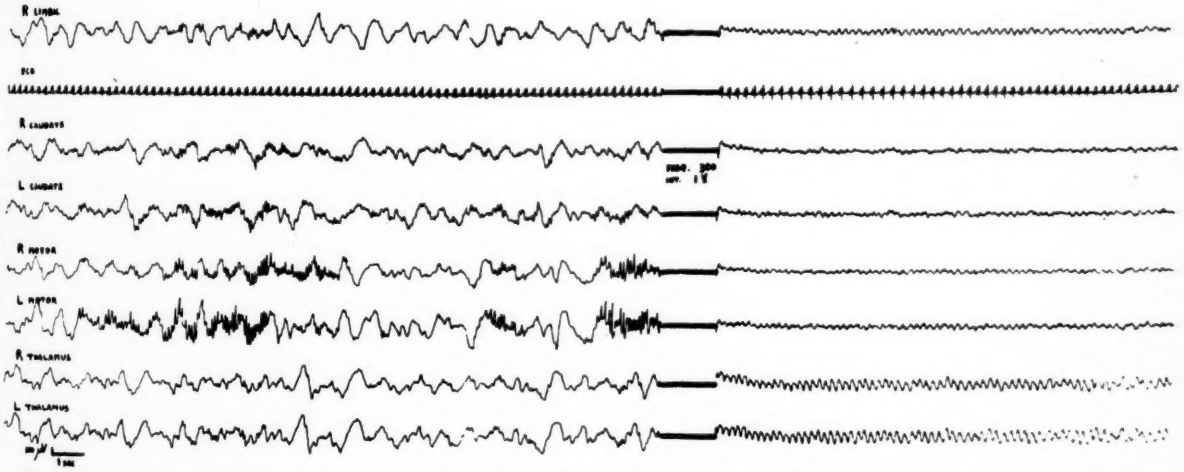

Figure 1. Control EEG patterns of the curarized unanesthetized rabbit. The leads are (from the top tracing to the bottom one): (1) right limbic cortex, (2) EKG, (3) right caudate nucleus, (4) left caudate nucleus, (5) right motor cortex, (6) left motor cortex, (7) right thalamus, (8) left thalamus. (See description in the text.)

sence of alerting EEG effect to sound stimulation and shortening of the duration of the alert pattern following other types of stimulation. Second stage of depression; absence of alerting EEG response to all three types of peripheral stimulation (sound, touch and pain), significant increase of the threshold to electrical stimulation of the midbrain reticular formation and marked reduction of the duration of the following EEG effect. At this stage there was also a complete antagonism to the alerting pattern induced by DFP and by intracarotid ACh. Third stage of depression; complete inhibition of the alerting EEG reactions to all types of stimulation including direct electrical stimulation of the midbrain reticular formation.

In the case of a stimulant action we also distinguished three progressive stages. First stage of stimulation; facilitation of alerting reaction to all stimuli, including the slighter ones, "spontaneous" alerting (following accidental noises) occurred easily, so that during a given time (15-20 min.), the record was occupied for about 50% of its length by the alert pattern. Second stage of stimulation; marked prolongation of the duration of the alerting effect following any stimulus. The EEG record was occupied for the greater part (80-90% of its length) by the alert pattern, few spindles and slow waves were present but for short periods only. Third stage of stimulation; permanently alert EEG pattern, complete absence of slow waves and spindles.

It is necessary to stress that both the depressant and the stimulant drugs act gradually and progressively; their effect increases with the magnitude of the dose. Therefore any clear cut subdivision into stages is arbitrary. We adopted them purely for purposes of description.

	High Voltage Slow Waves and 12-14 c/s Spindles DEPRESSION of the mesodiencephalic activating system				Cortical Fast Low Voltage Activity And 4-6 c/s Thalamic Rhythm STIMULATION of the mesodiencephalic activating system		
	Stage 3	Stage 2	Stage 1		Stage 1	Stage 2	Stage 3
	Complete inhibition of alerting responses to all stimuli.	Only direct electrical stimulation of the reticular formation can produce a short alerting response.	Absence of alerting EEG response after auditory stimuli. — Decreased duration of response to other stimuli.	Normal EEG patterns of the curarized not anesthetized rabbit.	Facilitation of alerting responses to all kinds of stimuli.	Marked prolongation of the duration of alerting responses to all kinds of stimuli.	Permanently alert EEG pattern.
ATROPINE	+++	+++	+++				
	10	3–6	1–3				
BENADRYL	+	+++	+++				++
	5–10	5–5	1–3				over 10–20
ARTANE	+	+++	+++				++
	4–5	2–3	1				over 10–20
PARPANIT	+	+++	+++				++
	5	2–3	1				over 10–15
CHLORPROMAZINE		++	+++				++
		3–6	0.5–1.5				over 12–20
GAMMA-PIPRADROL							++
				1–15			over 20–30
RESERPINE					+++	+++	++
					0.5	1	2
PIPRADROL					+++	+++	+++
					0.5–1	1–3	3–6
AMPHETAMINE					+++	+++	+++
					3	6	10
D F P					+++	+++	+++
					0.05	0.1	0.2

Figure 2. Table illustrating the effect of drugs upon the mesodiencephalic activating system. The number of plus signs represents the intensity of the depressant or the stimulating action of each drug. Three plus indicates that the corresponding stage of depression or of stimulation is fully obtained. Two or one plus indicates a more or less incomplete effect for the given stage. The figures represent mg/kg of drugs given by intravenous injections.

Results

The results of the experiments are summarized in the table of figure 2. In the table the results obtained in the present experiments are illustrated together with the action of atropine, of DFP and of other drugs discussed elsewhere.

(1) Chlorpromazine: Chlorpromazine was administered intravenously in progressively increasing amounts from 0.1 to 20 mg/kg. Beginning with doses of 0.5 mg/kg an inhibitory effect on the alerting reaction was noticed. The first stage of depression was reached between 0.5 and 1.5 mg/kg. With 3-6 mg/kg the depression was pushed further to the second stage (Figure 3). But additional amounts failed to obtain a deeper depression corresponding to the third stage. Instead larger doses approaching the lethal one of 15.0-20.0 mg/kg reversed the EEG effect: the signs of depression of the MDAS disappeared and instead excitation was observed.

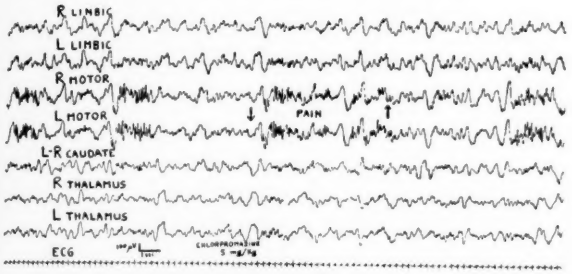

Figure 3. EEG pattern produced by 5 mg/kg of Chlorpromazine. Comparison with the control record (Figure 1) reveals the similarity of the Chlorpromazine-induced pattern to the normal sleeping pictur. Note the absence of the alerting reaction to pain stimulation (between arrows), sign of the depressant action of Chlorpromazine (in low doses) upon the mesodiencephalic activating system.

In the rabbit the minimum dose of Chlorpromazine giving behavioral sedation was 2.5 mg/kg. Chlorpromazine in the rabbit had a depressant action on the MDAS when administered in doses from one-half to twice the minimal effective dose. In that range the depressive effect was progressive, but was not complete because it never reached the third stage. In amounts from three times the minimal effective dose to the lethal one, Chlorpromazine reversed its action and excitation occurred.

(2) Reserpine: Reserpine was administered intravenously in progressively increasing amounts from 0.05 to 3.0 mg/kg. Up to 0.5 mg/kg Reserpine did not affect the alerting mechanism. There was no depression and even the slight stimulation of hand clapping produced an alerting reaction though excitation was not noticed. As the dosage was gradually increased (from 0.5 to 1 mg/kg) however, an excitatory action was brought about, and the second stage of stimulation was induced; prolongation of the duration of the EEG alerting reaction to any stimulation, and a lowering of the threshold for the electrical stimulation of the MBRF. Larger amounts of Reserpine (1.5-2.0 mg/kg) finally produced the third stage of stim-

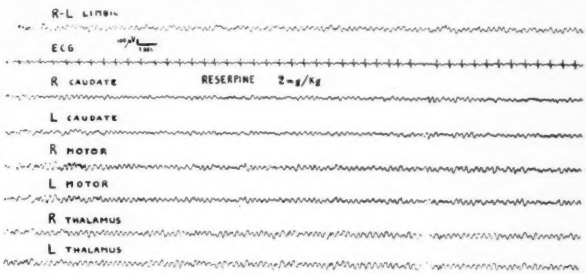

Figure 4. EEG pattern produced by 2 mg/kg of Reserpine. Note the resemblance of this picture to the normal alert pattern (Figure 1, right half), mainly in the absence of sleep spindles and of high voltage, slow activity and in the presence of a 4 c/s thalamic rhythm. Note also the bradycardia induced by Reserpine.

ulation (Figure 4). All the above-mentioned effects of Reserpine appeared with a latency of 20-30 minutes from the injection. The doses of Reserpine required for behavioral sedation in the rabbit ranged between 0.1-50 mg/kg, 1/10 to 1/2 of the acute intravenous lethal dose. Therefore, we may say that Reserpine administered in amounts that produce sedation had a stimulant effect on the alerting mechanism when the dose (0.5-2 mg/kg) was relatively high or no effect whatsoever when the dose (0.1-0.5 mg/kg) was relatively low. There was no evidence of depression of the alerting mechanism caused by Reserpine in the amounts used in our experiments.

(3) Frenquel (MER-17): Frenquel was administered intravenously in progressively increasing amounts from 1 to 45 mg/kg. We found that doses of Frenquel above 30-45 mg/kg are lethal for the rabbit in an experimental condition. When Frenquel was injected in doses certainly below the lethal

range no effect was noted on the alerting mechanism, neither a depression nor a stimulation. When Frenquel was given in lethal amounts, death was preceded by a period in which the EEG showed definite signs of excitation of the MDAS.

(4) Pipradrol (Meratran): Pipradrol was administered intravenously in progressively increasing amounts from 0.15 to 15 mg/kg. The effect of Pipradrol on the alerting mechanism was unidirectional and consisted of a progressive stimulation of the activating system. With doses around 0.5 mg/kg the first stage of stimulation was reached; with 1-3 mg/kg the second stage, while with doses between 3-6 mg/kg the third stage was attained (Figure 5).

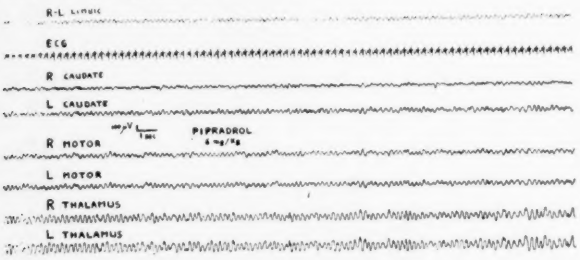

Figure 5. EEG pattern produced by 6 mg/kg of Pipradrol. This record is essentially one of alertness (compare with right half of record in Figure 1): the sleep spindles and the high voltage slow activity are absent; a thalamic rhythm (5 c/s) and low voltage fast activity in the motor cortex and in the caudate nuclei are dominant.

The LD 50 of intravenously injected Pipradrol for the rabbit was 15 mg/kg, and the range of doses which evoked an increase of behavioral activity in experimental animals lay between 2-20% of LD 50. We observed that amounts of Pipdradrol above 1% of LD 50 produced stimulation of the MDAS in the rabbit. The effect was progressive and became maximal with doses between 10-40% of LD 50.

Discussion

The EEG of patients in whom anxiety is a major symptom shows a large amount of fast activity and poor alpha organization in a high percentage of cases.[4,8,9,10] This finding of a tendency to desynchronization may be related to a condition of overactivity of the MDAS. A similar change can be produced by pharmacological agents. DFP administered to human subjects, normal individuals and schizophrenic and manic depressive patients, produces, beside insomnia and other symptoms, a psychological modification that consists primarily of anxiety and restlessness.[13,30] Since DFP is a specific stimulant of the MDAS it is reasonable to suggest that anxiety and overactivity are evoked when the MDAS is rendered hyperactive.

Schut and Himwich[31] have found that Pipradrol increases the normal and abnormal activity of psychotic patients and increases anxiety when it is present. We have seen that Pipradrol, like DFP, is also a stimulant of the MDAS. Amphetamine, another stimulant of the MDAS (Rinaldi and Himwich[29]), also evokes anxiety. Thus the actions of both Pipradrol and Amphetamine are compatible with the hypothesis that the hyperactivity of the MDAS is associated with anxious states.

Chlorpromazine as we have seen is a depressant of the MDAS, at least in low dosage, and is a good sedative which relieves anxiety.[17,1,6,32] These actions are in agreement with the hypothesis that the depression of the MDAS relieves anxious conditions.

But this deduction cannot be generalized, as shown by the effect of Reserpine. The drug is a sedative and also a corrective for anxiety.[34,15,35] However, Reserpine is not a depressant but a stimulant of the MDAS. So we must conclude that the hyperactivity of the MDAS by itself cannot be held responsible for the production of anxious states. If we compare the pharmacological activity of Reserpine and Chlorpromazine we find that while they have opposite effects on the MDAS, they exert similar actions on the hypothalamic centers. Reserpine produces changes in blood pressure, heart rate, pupils, and intestinal motility that are concordant with a condition of parasympathetic hyperactivity: myosis, bradycardia, increase of intestinal motility, decrease of blood pressure, especially if the blood pressure is elevated.[3,23] But this picture which is also one of sympathetic hypoactivity, is not produced by a blocking of ganglionic transmission in the sympathetic ganglia, nor is it due to an antiadrenergic effect on sympathetic endings because the action of sympathomimetic substances like adrenaline and noradrenaline is not depressed but on the contrary is enhanced. Neither are the vegetative effects

due to a stimulation of the peripheral parasympathetics because Reserpine does not potentiate the action of ACh. The blood pressure effect, moreover, is not inhibited by atropine, nor by cutting the vagi and the depressor nerves.[3] Reserpine does, however, depress the pressor reflex responses due to stimulation of the central vagus and of the sciatic nerve.[3] Thus the picture of sympathetic hypoactivity seems to be due to inhibition of the hypothalamus. Chlorpromazine differs from Reserpine for it produces autonomic changes that are partially due to peripheral effects.[5,24] It has an adrenalytic action, blocking the depressor and the hyperglycemic effect of epinephrine. It possesses a ganglionic blocking property, and also atropine-like effects. Besides these peripheral autonomic actions, Chlorpromazine is also a depressant of the CNS. It produces a fall of body temperature and a decrease of the metabolic rate. These changes indicate that Chlorpromazine exerts a restraining action upon the hypothalamus. Chlorpromazine has other central effects of a depressant type including the potentiation of the action of narcotics such as barbiturates. Thus both Reserpine and Chlorpromazine inhibit the hypothalamus. Accordingly, it seems that the therapeutic value of a drug against anxiety does not depend on the inhibition of the MDAS, but rather on the depression of the hypothalamus. (In regard to the hypothesis that the activity of the hypothalamus is related to the production of anxiety, see also Gellhorn.[11])

If the hyperactivity of the hypothalamus is associated with the production of anxiety, why does anxiety accompany hyperactivity of the MDAS? We have seen in our previous experiments[27,28] that electrical stimulation of the BSRF, not only produced EEG alerting, but also other effects. Two very prominent effects are the dilatation of the pupils and the temporary rise in blood pressure, signs of a sympathetic discharge. The same effects are caused, and this is a paradoxical action, by the injection of ACh which we know stimulates the BSRF. This paradoxical action of ACh involves an excitation of the hypothalamus comparable to that one described by Dikshit following intraventricular injections of ACh.[7] Thus, stimulation of the MDAS is accompanied by hyperactivity of the hypothalamic centers, and chiefly those involved in sympathetic activity. The effect resembles the sympathetic hyperactivity that accompanies hypothalamic or sham rage. The pupillary and blood pressure signs evoked by painful stimuli may be another instance of a sympathetic discharge following hypothalamic arousal caused by hyperactivity of the MDAS. These facts indicate that the MDAS can excite a hypothalamic hyperactivity which in turn may be responsible for the production of anxiety. Though the MDAS impinges upon the hypothalamus, the two systems do not necessarily behave as a functional unit. In fact a distinction can be made between the two systems by the use of Reserpine for it stimulates the MDAS while depressing the hypothalamus and producing apparent signs of central sympathetic hypoactivity. The stimulant effect may explain how Reservine can produce sedation without enforcing sleep.

Differing from Reserpine, DFP gives rise to hyperactivity of the MDAS without depressing the hypothalamus. The unimpeded action on the MDAS explains why DFP evokes anxiety. The stimulation of the MDAS is probably also involved in the production of anxiety with Pipradrol and Amphetamine. With Amphetamine, however, the direct sympathomimetic action must also be taken into consideration.

The sedative action of Chlorpromazine is probably related to the depression of the hypothalamus and also in large doses to that of the MDAS.

In the case of Frenquel the MDAS remains unaffected, but sedation occurs. Preliminary clinical studies with Frenquel indicate that the sedation is not accompanied by those prominent actions of the vegetative system that Chlorpromazine and Reserpine display. We cannot therefore at this time invoke either an inhibition of the MDAS or of the hypothalamus to explain the sedative action of Frenquel.

Recent reports on the clinical usage reveal that Chlorpromazine[2,12,22] in large doses and Reserpine (personal observations) can produce Parkinson-like symptoms such as tremor and rigidity. In our study Reserpine stimulated the MDAS and Chlorpromazine

with dosage above 5-6 mg/kg reversed its depressive action on the MDAS and turned it into stimulation. As we pointed out in a previous publication,[29] drugs that stimulate the MDAS evoke Parkinson-like symptoms. We have now another confirmation of this fact in the results obtained on human patients. The untoward stimulating effect of Reserpine and Chlorpromazine can be prevented and corrected by the administration of atropine or atropine-mimetic drugs like Artane, Parpanit and antihistaminics like Benadryl.

Nonetheless the use of these antiparkinson drugs to treat the Parkinson syndrome following the administration of high doses of Chlorpromazine and Reserpine may be contraindicated. The synthetic antiparkinson atropine-mimetic drugs mentioned above show, like Chlorpromazine, reversal with high doses changing from inhibition to stimulation of the MDAS. Therefore their action might summate with the MDAS-stimulant effects of Chlorpromazine and Reserpine and result in a worsening of the Parkinson syndrome. Probably this danger does not exist with atropine, the action of which is depressant of the MDAS in all doses.

The present studies reveal a possible therapeutic value of atropine and atropine-like substances in psychiatry. Even if these drugs do not depress the hypothalamus, they can relieve it from the influence of the MDAS which they paralyze. They, therefore, may be of value in the treatment of anxious and excited conditions either by themselves or in association with drugs that directly depress the hypothalamus.

Summary and Conclusions

1. Studies of Reserpine, Chlorpromazine and other drugs were made in order to compare their EEG effects with their ability to influence normal and psychotic behavior.

2. It was found that the EEG changes produced by these drugs are brought about either through stimulation or depression of the mesodiencephalic alerting system.

3. Drugs that stimulate specifically the alerting mechanism, such as Amphetamine, Pipradrol and DFP, increase anxiety.

4. Drugs that alleviate anxiety, such as Reserpine and Chlorpromazine, do not necessarily inhibit the alerting mechanism, but they depress the hypothalamus.

5. The effect of drugs on anxiety seem therefore to be carried on by a bipartite mechanism (a) the brainstem - thalamic alerting system and (b) the hypothalamus.

6. The hypothalamus is probably the more important in regard to anxiety, since alleviation of anxiety is a property of drugs that depress the hypothalamus.

7. The activity of the hypothalamus, however, may also be diminished when the alerting mechanism is depressed because the flood of impulses impinging upon the hypothalamus is reduced.

8. On the other hand, overactivity of the alerting mechanism produces anxiety through secondary stimulation of the hypothalamus. This mechanism is rendered ineffective when the hypothalamus is depressed.

9. In placing both structures in their proper functional relationship we conclude that the effect of a drug upon anxiety is the resultant of an integrated action on the alerting mechanism and the hypothalamus. The production of anxiety is associated with stimulation of hypothalamic areas, and the alleviation of that symptom with their depression. The essential change therefore occurs in the hypothalamus. This may be brought about by influencing that portion of the diencephalon either directly or indirectly, the latter by affecting the function of its afferent supply afforded by the mesodiencephalic alerting mechanism.

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The Value of Orienting Therapy to Purpose

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A university student was brought into our ward by the police. He had been caught breaking into an apartment house. The break in had been reported to the police by a person living next door who had heard the young man rattling screens, knocking over things, and making considerable noise. When the police came up the student ran away. He could have escaped but instead ran in a circle and was caught by the police. We could apply to this young man's behavior many motives which depended on his life experience, but there also seemed to be a very obvious purpose and that was to be arrested and taken into custody.

It is necessary at this point to discuss three terms which will be used throughout this paper. The first is the term need. This is considered as a disturbed equilibrium in the behavior of an organism appearing as increased activity or tension. This behavior results from effect of a stimulus which becomes the object of a reaction whose purpose is to put a stop to the action of the stimulus. A need for food is ended when the stimulus food is obtained. Need, object, and purpose then are part of every reaction.

Any form of human behavior, regardless how simple or how complex, has purpose, has meaning, and is done to bring something about, to achieve some goal. The results sought may be very simple and obvious, or may be devious and far removed. It is of value in any attempt at therapy of aberrant and pathological behavior to consider what the patient is trying to do, since frequently even if we don't know why a patient does as he does, or how he expects to accomplish it, nevertheless we can bring about the results he seeks and by so doing permit him to put a stop to his irritating behavior. Insight into why a patient reacts is of value, to know what goal he seeks is even better, but the only way to bring a reaction to an end is to have the goal accomplished. This may be done without the knowledge of why the reaction occurred or what it was after.

When one attempts to estimate the objects sought by the patient, it is well never to underestimate the magnitude of the object sought, or the number of objects the patient seeks. There is a tendency to belittle people who manifest "crazy reactions." They are said to be immature and their reactions a sign that they are weak or sort of feebleminded. I do not hold to the thesis that the mentally ill are always superior people, but I do know they have many superior traits and that it is a serious mistake to approach them as if they were inferior. This attitude on the part of the physician is often fostered by the patient. Nothing could be more serious than to fall in the trap.

When St. Paul was on trial in Caesarea before King Agrippa, Festus, the prosecuting attorney, when he saw he was losing the case, said in a loud voice, "Paul, you are mad, much learning has made you mad." This appeal to insanity as a defense is used today by us as therapists, in the face of potentials that we sense but understand only sufficiently to fear. We say the patient is regressed as if it were a turning backward to a more infantile state when all the time the patient is using regressions as part of an ongoing reaction. Regression has a purpose or it would not be used.

It is best to apply the remark of Festus in another way. True, the apparent madness is the product of too much learning. The patient has tried other ways and now has learned that this method is the most effective one for obtaining the sought-for goal. Aberrant reactions are products of social learning just like so-called normal forms of behavior. We speak of such reactions as being economical, but we seem to forget that the statement is true.

The idea that anxiety or the inability to take anxiety is the central core of most neurotic and psychotic reactions seems to me to be an obvious belittlement of people. Many of us stand anxiety reactions day after day without using obviously pathological behavior. Yet we say that others of us go through hell because of some bizarre and strange be-

havior because they can't take anxiety. It doesn't make sense. Certainly there are many cases when anxiety is definitely present and others when obviously there is a need to escape anxiety; but I see no reason for hypothecating the dread of anxiety as a cause when there is no evidence of its presence. It seems to me to make more sense to say that the patient is acting as he does, to bring things about. He wants to be seen by someone as the person he is. He wants to bring about changes in the behavior of loved ones, in his family, or in the community. He knows from experience that this is the only way that he can do it.

I have a patient in the hospital now because he has what he calls a "suicidal mania." He has a thought of jumping out of windows, of breaking glasses to cut himself. He has a mother in Florida who has dominated him for thirty years. When he came in the hospital he wanted everyone to promise not to inform his mother, since she was very religious and to think him suicidal would upset her. Next he asked me rather slyly, "Doctor, did you write my mother about my illness without letting me know?" When I assured him that I would not do anything of the sort without letting him know, he wrote to her himself. I asked him why. He then came to see that his reaction had very little purpose unless his mother was upset. One of its objects was to disturb mother, but this seemed to be only one of the objects. He had a great deal of anxiety which reached almost panic proportions but which he dropped immediately when he found that he and I could relate on a warm, friendly basis. To have someone to relate to, was another need. He still has other needs that are not solved, so his obsessions continue.

Anxiety undoubtedly does arise from conflict. Certainly it does denote the return of the repressed, but also anxiety or the expression of anxiety has purpose in its own right. It behooves the psychiatrist to look into the reason why the patient shows anxiety in his presence. The patient is doing it because he wants something from the psychiatrist he is not getting, or he is using this disturbing reaction to bring something about in which the patient feels that the psychiatrist can play a part. Perhaps the anxiety is used to test the depth of the therapist's involvement or to see if the therapist can be side-tracked. As the real purpose of the reaction becomes more obvious or the doctor-patient relationship more threatening, the patient becomes more anxious. Indeed this can continue until the anxiety will block communication provided the therapist is so foolish as to think the anxiety is dangerous, and backs away. If he looks at it as a purposive maneuver and indicating strength rather than weakness, if it means come on rather than stop, the disturbing anxiety leads on to definite goal solving.

The purpose of an alcoholic debauch in a problem drinker is something that is difficult to discern. It seems to me that there are usually two purposes. One is a long standing one. The alcoholic is usually a person who on the surface is very affable and kind. He is a sweet talker that loves everybody. If you listen closely, however, or get him to trust you sufficiently, you can feel the generalized hate that he carries just below the surface. Many alcoholics are angry people, but they have to get drunk to show their anger. The other purpose of the alcoholic spree has to do with the present attack. The usual spree is arranged for a definite purpose. It is frequently the meanest and the most diabolical form of behavior that the patient could think of at that moment, if you consider that he is trying to be mean and diabolical. He is after a loved one, or a hated one, and his anger is so great that he cares nothing about himself. He wants this close person to see his anger and to feel that something must be done.

A man came in after a severe drinking bout. His reaction was delirium tremens. He was his wife's second husband. She would not let him visit his people and wanted him to have little to do with them since she felt them inferior. He was long suffering and patient, but this attack made his wife listen to what he had to say. After the reaction was over he told his wife what he was and was not going to do. He has visited his father for the first time since the marriage. It would seem that this attack had accomplished its purpose. Of course such superficial business does not explain why he has

to use this method of behavior, nor does it guarantee that he won't use it again.

Case No. 298636 came in suffering from acute alcoholic hallucinosis the other day. We found his blood magnesium low and gave him magnesium intravenously. On the morning of the third day he was up and ready to leave the hospital. His cure seemed remarkable. We thought it was the magnesium. He said, "No, Doc, my wife lives in New Jersey and I live in Virginia. She came down here against her will. Recently she has been determined that we would have to move back to New Jersey. Last night when she visited me she said she had changed her mind and agreed to stay in Virginia. 'Doc,' he said, "that is what made me well, not the medicine." Perhaps he was right.

The case of agitated depression is able to drop his reaction in an astounding fashion. If only the family is present, he is terrifically disturbed. He is overactive and apparently suffering terribly. When a stranger comes in he may suddenly become very pleasant, charming and apparently entirely free from his previous reaction. However, he resumes his pattern of behavior as soon as the stranger is gone. This rapid shift shows that he is using his agitated depression to do something with his family and also that he wanted to accomplish something else with the stranger. If then this patient uses this depressive reaction in your office, he is doing it because he wants this reaction to accomplish something with you. He can drop this with you if you can show him he does not need it to have you see him, or if you show him you have no use for it and can't be made sorry for him. He acts toward you like he does toward the stranger, dropping the depression.

Case No. 199573, a man of 55, entered the hospital in a depressed condition. He had been in once before. At that time his depression was arrested by electroshock. On this occasion intensive psychotherapy was attempted. He developed insight. He knew that the attitude of his foster parents, Uncle John and Aunt Mary, had a great deal to do with his use of the depressive reaction. Suddenly Uncle John did an about face. He began to demonstrate a great deal of understanding and a genuine love for our patient. This change of attitude was backed up by deeds. The patient was able to drop his depression. When he was seen three weeks later there was still some evidence of the use of the reaction, but he was working every day. The relation with Uncle John was of no major concern but there was still something to be done regarding the attitude of the wife and his relationship to his physician.

There is evidence to show that when someone has the power to enter into the fantasy life of the schizophrenic to such a degree that the patient feels that his fantasy is shared, a true relationship based on a give-and-take of affection can be formed. The formation of this relationship takes away the lonesomeness, the unhappiness and the unwanted feeling. In its place comes a feeling of warmth and happiness which is new. Such a reaction in these people who have been disturbed so long, has nothing to do with content or with insight. A present day need for sharing is answered and something happens immediately. I don't say that all those things that motivate the schizophrenic reaction are accomplished or that the reaction is immediately dropped. Frequently, however, there is a decided change and the reaction does drop until someone in the environment, mother, sister or just the culture calls for a renewal of the abnormal behavior. What I am trying to say is that there is an ever present need for sharing at the basis of the schizophrenic reaction, which if satisfied, brings an immediate change in behavior. The feeling according to the patient is one of joy, calmness and peace. Apparently very much like an evangelical experience when a person feels the presence of a loving God. One patient described this experience of God's presence to me today as being one of great joy which spread throughout the body. Some therapists are convinced that if the schizophrenic has this experience with someone, he can go on to accomplish all his goals. I must admit that I have not seen this happen. I must say I doubt if love is enough for the continued dropping of the schizophrenic reaction, because there are too many things to be brought about and the schizophrenic reaction is a learned one, which has often been effective. It seems to me the schizophrenic would be forced to return to his old

behavior in his attempt to straighten out loved ones, family and the community. On the other hand, if a few of the purposes of the reaction are accomplished there is a possibility that the patient can go on his own to satisfy his other needs.

The hypochondriacal reaction, the nihilistic delusions of the involutional, and the paranoid behavior of the schizophrenic are dropped in the presence of the therapist provided the therapist can prove to the patient that this form of behavior has no purpose in relationship to him. This does not mean that the patient will not take up the reaction again if someone else comes into the office or if he gets with family or friends. These shifts in behavior have a great deal of value when considered from the point of view of what the patient is trying to accomplish at that moment, and also as indications of what he is trying to accomplish by his whole reaction. They emphasize especially the value of the here and now. We are inclined to think that needs exist in the past. It is true that the past can qualify a need, but the need can only exist in the present. The need-satisfaction sequence often takes time for fulfillment, thus the sequence has to do with the future. Therefore, purposes stretch over into the future, but the past is dead as far as both need and purpose are concerned.

We learn about needs, about types of reaction, and probable goals, from our study of the past. Patients have memories, they have skills, and have patterns of behavior, all of which have their influence on what goes on now. But also there is something new each day that is the need, which is much the same today as yesterday but not quite, since there is always something added. There is also the goal which changes with the need. This means that if from our study of the past, or if from the powers vested in us as therapists today, we can bring about the satisfaction of that need today, the need-satisfaction sequence will reach its goal and there will be no further purpose in the existence of the reaction. This is the hopeful aspect of psychiatry. Each day brings forth the possibility that the right thing may be done by the right person at the right time. If this happens, then the acute reaction or the long chronic reaction may be dropped, at least in part, and the potentials of the crippled patient liberated.

Need-satisfaction sequences modify and multiply each day they exist in an unsatisfied state. The therapist therefore frequently finds that he is incapable of doing a complete job, since not only is *he* involved, but it is necessary to bring about changes in the home and the community. Group therapy, multiple therapists, and therapeutic teams which have as their aim the accomplishment of the patient's goals can succeed where the individual fails. The recognition of each and every purpose is impossible. However, such recognition is not necessary since if the goal is reached the reaction ceases.

In conclusion, all behavior is purposive, since it occurs in response to needs which must be satisfied. The need-satisfaction sequence is modified by the past, but is always in the present and future. There is always value in what goes on now in the therapeutic situation. Anxiety frequently has present purpose as do other forms of behavior. Behavior distortions are kept alive by unsolved needs which may have to do with many different relationships, and these behavior distortions will cease when the needs are satisfied and the purpose of the reaction fulfilled. There is always hope for this achievement of goals; and the therapist should at all times consider not only why the patient's behavior existed in the past, but what is its purpose now, and in relationship to the therapist.

Large Doses of Chlorpromazine in the Treatment of Psychiatric Patients

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Since the initial report of the French psychiatrists on the effectiveness of Chlorpromazine in the management of anxiety, tension and psychomotor excitement, this drug has been carefully studied by numerous investors.[1] All are in agreement about the efficacy of this drug in such conditions as manic reactions, catatonic excitements, panic states, and severe anxiety reactions. The concensus of opinion of those reporting on Chlorpromazine is that the majority of patients respond favorably to doses ranging from 100 mgm. to 300 mgm. daily. At present, there are no published reports of clinical observations on the response of patients to massive doses of this drug, although several authors have alluded to their observations in individual cases.

This is a brief report on the effect of large doses of Chlorpromazine, 700 mgm. to 2500 mgm. daily, administered to a group of 25 hospitalized psychiatric patients. Large doses were used for the following reasons: (1) to determine if large doses are more effective than the usual dosage range of 100 mgm. to 300 mgm. daily; (2) to determine if toxic effects are more likely to occur with large doses; and (3) to determine what effect, if any, large doses would have on the central nervous system. The drug was administered intramuscularly and orally. The duration of treatment varied from two weeks to six months. The temperature, pulse and blood pressure was recorded. Psychiatric and neurologic examinations were repeated frequently, in some instance daily.

The response of these patients to large doses of Chlorpromazine was quite varied. Initially all of them were somnolent but could be aroused easily for meals and for psychiatric and neurologic examinations. In the absence of external stimuli these patients would return to their somnolent state. Concomitant with this somnolent state produced by large doses of Chlorpromazine, all of these patients manifested some degree of catalepsy. Both the somnolence and catalepsy disappeared when the drug was reduced or discontinued.

Those patients receiving the drug intramuscularly had a slight elevation of temperature, up to 101 degrees in one case. This febrile reaction subsided within five days. It was noted only in those patients receiving the drug intramuscularly and was probably due to a local tissue reaction at the site of injection. The pulse rate either remained within the range of normal variation or else a slight tachycardia was recorded. This latter reaction usually occurred within twenty minutes to one hour after medication. There was an initial drop in blood pressure of 20 to 40 mm of Hg. with a tendency for the blood pressure to gradually return to the pretreatment level even though treatment was continued.

Constipation occurred in every patient. Laxatives usually sufficed to relieve this although practically all patients required at least one enema. An apparent polyuria occurred in every case during the first week of treatment, although this was not verified by an intake-output chart. Generally, the urine was darker in color, especially when the patient had not voided for several hours. This apparent polyuria and discoloration of the urine did not persist beyond the first week or two of treatment, although the urine would be darker than usual sporadically.

The appearance of the patients receiving large doses of Chlorpromazine changed within the first three days. All of them had a masklike facies. Their face and eyes became immobile as they laid quietly in bed. Pallor was pronounced. All movements were slow and their speech was monotonous as well as slow. On standing they had a drooped appearance and they walked on a wide base. One patient developed the picture of paralysis agitans within 48 hours after being

started on 700 mgm. a day. This patient, a 29 year old white male, with a severe obsessional neurosis, in addition to the pale, masklike facies, exhibited muscular rigidity with flexion of the body, dysarthria, dysphagia, salivation with drooling and disturbance in gait. When he went to sit down, he "drooped" into the chair. His speech was monotonous. All his associative movements were slow. The psychiatric examination did not disclose any psychic change other than those for which he was being treated. There was no impairment of the intellect. There was a slight tremor confined to the head and arms. No cogwheel phenomena could be demonstrated. There were no pathological reflexes.

This Parkinsonian-like reaction persisted for five days. It caused considerable alarm among the nurses and the patients' relatives. It did not progress beyond the picture described above even though Chlorpromazine 700 mgm. daily was continued. After five days the dosage of the drug was reduced to 500 mgm. a day and by the eighth day of treatment this Parkinsonian-like reaction subsided completely. The patient became ambulatory and experienced no untoward side effects, although he continued to take 350 mgm. to 500 mgm. daily for the next three months. He is now taking 200 mgm. a day and has been on Chlorpromazine for five months.

Aside from the masklike facies, the slowness of movement and the monotonous speech, none of the other patients in this series developed any other symptoms suggestive of Parkinsonism, except one. This patient, a 68 year old white woman, with a severe involutional agitated depression received doses of Chlorpromazine ranging from 300 mgm. to 1000 mgm. daily. While receiving 1000 mgm. a day this patient developed a Parkinsonian-like tremor confined to the right arm. This neurologic finding disappeared when the drug was reduced to 800 mgm. daily. For a period of four months this patient received 700 mgm. to 800 mgm. daily without any neurologic changes that were detectable. Chlorpromazine was abruptly discontinued when her relatives finally consented to EST which produced a prompt remission from her psychosis. This abrupt discontinuation of Chlorpromazine did not cause any observable withdrawal reaction, unless this was masked by the shock therapy.

The masklike facies persisted as long as the patients received large doses of Chlorpromazine. Reduction of the daily dosage below 500 mgm. resulted in a disappearance of this facial expression within a few days. Aside from the neurologic findings in those patients who developed a Parkinsonian-like reaction, no gross neurologic changes were detected in patients on large doses of Chlorpromazine.

Likewise no mental changes attributable to this drug, with one exception, were observed. This exception is that if large doses were given for more than two to three weeks, some patients developed a depression. Usually this depressed affect abated with the reduction or the discontinuation of the drug, although in one case the depression persisted. In this case EST terminated the depression. This occurrence of a depressive reaction with Chlorpromazine illustrates the reciprocal relationship between anxiety and depression in some psychiatric patients.[2] Clinically the effect of Chlorpromazine on anxiety seems to be similar to that produced by non-convulsive electrostimulation and insulin sub-coma therapy. All three of these treatment modalities can cause a reduction in anxiety, while at the same time enhancing depression. Those patients who developed depressions while taking Chlorpromazine and who were treated with EST experienced a return of some anxiety following shock therapy. This resurgence of anxiety in some shock treated patients is a common experience.

Based on the experience gained from this study, as well as the results obtained in a much larger series of patients treated with Chlorpromazine reported elsewhere, it is concluded that large doses of this drug are no more effective, except in the minority of cases, than the usual dosage range of 200 mgm. to 300 mgm. daily for the disturbed patient.[3] To administer large doses of Chlorpromazine with the hope of increasing therapeutic effectiveness has been futile.

Because of the appearance of a Parkinsonian-like reaction in some patients receiving Chlorpromazine, it was decided to give this drug to patients with Parkinsonism. Two patients with Parkinsonism, one post-encephalitic, the other arteriosclerotic in origin, were treated with Chlorpromazine. These patients derived no benefit from Chlorpormazine, nor was their Parkinsonism made worse. This corresponds to the experience reported by others.[4]

In my experience large doses of chlorpormazine do not cause any serious toxic effects. Jaundice did not occur in any patient receiving more than 500 mgm. daily. Jaundice has occurred in patients on much smaller doses. Likewise, although two patients in this series developed a Parkinsonian-like reaction, this same reaction has been observed in patients on smaller doses.[5] Although none of the patients in this series developed respiratory infections, such illnesses have occurred in other patients on Chlorpormazine and the possibility of respiratory infections in patients on large doses of this drug exists. If large doses of Chlorpormazine can cause liver damage, such was not observed clinically in this series of patients, although extensive laboratory studies were not done, mainly because there was no clinical indication for such studies.

Whenever a patient is to receive large doses of Chlorpromazine, he should be hospitalized. Close medical and nursing supervision is absolutely necessary. Strict bed rest should be enforced, even though the patient, at least in the beginning of treatment, usually is somnolent and unable to get out of bed. Temperature, pulse and blood pressure should be recorded. Frequent psychiatric and neurologic examinations are necessary for the early detection of depressive reactions and the Parkinsonian-like reactions observed in this series of patients. In the event a depression, a Parkinsonian-like reaction, or any other toxic reaction should develop, these usually subside when the dosage of the drug is reduced. If any severe reactions develop, the drug should be discontinued, at least temporarily.

Summary

Large doses of Chlorpormazine were administered to 25 hospitalized psychiatric patients. The dosage range varied from 700 mgm. to 2500 mgm. daily. The duration of treatment was two weeks to six months. No serious, persistent toxic effects were observed in the patients treated. One patient developed a Parkinsonian-like reaction of moderate severity while receiving 700 mgm. daily. This reaction subsided when the dosage of Chlorpormazine was reduced to 500 mgm. daily. This patient has continued to take Chlorpromazine for five months without any undesirable side effects appearing. The other patient developed a transient Parkinsonian-like tremor of the right arm while taking 1000 mgm. daily and this subsided when the dosage was reduced to 800 mgm. daily which the patient took for four months without any undesirable side effects.

The clinical picture of patients on large doses of Chlorpromazine resembles that observed in monkeys and cats following bilateral hypothalamic lesions.[6] The patients are somnolent, exhibit some catalepsy, have masklike facies, an apparent polyuria, and slowness of associated movements. These symptoms abate when the dosage of the drug is reduced or the drug discontinued.

One undesirable effect of large doses of Chlorpromazine is the possible production of a depression. Fortunately, this depressive reaction is usually not serious. It abates when the drug is discontinued or the dosage reduced. When the depression persists EST promptly relieves it.

Large doses of Chlorpromazine are no more effective than the usual dosage range of 200 mgm. to 300 mgm. daily, except in the occasional patient. To administer large doses with the hope of increasing the therapeutic effectiveness has been futile.

In two cases of Parkinsonism, one post-encephalitic, the other arteriosclerotic in origin, Chlorpromazine was of no benefit and it did not make the Parkinsonism worse.

Large doses of Chlorpromazine should be administered only to hospitalized patients under close medical, psychiatric and nursing supervision.

Author's Note: Chlorpromazine is commercially prepared under the name Thorazine. The chlorpromazine for this study was generously supplied by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

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A Follow-up Study of Psychiatric Patients Treated with Carbon Dioxide Inhalation Therapy

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A survey of the literature reveals that a number of attempts have been made to evaluate the efficacy of carbon dioxide inhalation therapy. Frank,[1] fully recognizing the fact that different authors report varying results, that diagnostic terminology is confusing, that methods of assessing improvement are not clearly stated, and that controls and follow-up studies are lacking, attempted to apply statistics to eleven published reports consisting of heterogeneous data, and thus summarized the treatment results of 238 non-psychotic patients. He arrived at an over-all improvement rate of 61%, with rates ranging from 22% to 90%. It is of interest that in Frank's statistical survey, a comparison of patients receiving carbon dioxide with and without concurrent psychotherapy, revealed an identical improvement rate of nearly 60%. Frank emphasizes that in order to determine whether or not improvement is lasting, long-term follow-up studies and control groups must be employed, to evaluate treatment results objectively. He is especially concerned with the spontaneous improvement rate in psychoneurotic patients and quotes the figure of 68%, cited by Landis in a state mental hospital survey. Moriarty[2] reported on evaluation of clinical results with carbon dioxide therapy in 100 neurotic patients, with a follow-up of from 12 to 18 months. His over-all results revealed 42% much improved, 39% improved, and 19% unimproved. Patients with anxiety states, phobic reactions, character neuroses, and psychosomatic reactions showed a generally good response in his experience. In a discussion of his paper, LaVerne[3] reported 55% clinical improvement in 50 unselected patients, using the rapid coma, single breath technique, whereas in a group of ten control patients, treated with nitrous oxide coma, only 20% of the patients were improved. A comparative study between 50 patients with anxiety or depression receiving carbon dioxide and psychotherapy, and 50 patients treated with psychotherapy alone, was reported by Hargrove, Bennett and Steele.[4] These authors found that two-thirds of the patients treated with carbon dioxide and psychotherapy showed no change in their condition and that only one-third improved.

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In their control group, treated with psychotherapy alone, three-fourths improved while only one-fourth showed no change. It was also noted that patients treated with psychotherapy alone improved with fewer treatments. They concluded that psychotherapy strengthens the patient's defenses, whereas carbon dioxide causes explosive abreaction which cannot be integrated into the patient's defense mechanisms, causing psychotherapy to become more difficult and delaying or preventing recovery.

In a previous investigation[5] 38 non-psychotic male veteran patients who received carbon dioxide therapy and concurrent psychotherapy were compared with a closely matched group of 38 patients who received only psychotherapy. Both groups were tested with the Minnesota Multiphasic Personality Inventory before and after treatment and their mean profiles were compared. Both groups showed significantly reduced scale scores following treatment, reflecting clinical improvement, but no statistically significant differences were found between the profiles of the carbon dioxide therapy group and the control group. This suggested that as a group the patients treated with carbon dioxide and psychotherapy do not differ after treatment from a group of psychoneurotic patients treated with psychotherapy but not receiving carbon dioxide. There was no difference in the length of hospitalization for the two groups (56 days). As a result of these findings, the question as to whether or not the addition of carbon dioxide to the treatment regime was of any value was raised, but attention was called to the fact that the patients who received carbon dioxide had been initially selected because of their resistance and inaccessibility to psychotherapy.

The present follow-up study was made in an attempt to cross-check these results from a different point of view by evaluating sociological and longitudinal aspects. In the original study there were 38 patients in each group, matched on the basis of diagnosis. These included 23 anxiety reactions, eight psychophysiological reactions, four depressive reactions, two character disorders and one phobic reaction. Seven patients who could not be exactly matched on the basis of their diagnoses, including one with anxiety reaction, one with depressive reaction, one with conversion reaction, one with psychophysiological reaction, two patients with chronic alcoholism, and one with simple schizophrenic reaction, were retained in the experimental group to maintain the size of the sample. At the time of the follow-up the experimental group, consisting of 45 patients, had a mean of 19.4 months since discharge from the hospital, with a range of from 12 to 28 months. The control group of 38 patients had a mean of 43.5 months since discharge, varying from 14 to 81 months.

A questionnaire was used to determine post-discharge adjustment. This questionnaire was a revised form of one previously constructed by Jenkins,[6] which he had found yielded useful results when applied to a follow-up study of patients with paranoid schizophrenia. Included in the questionnaire were 13 items relating to health and symptoms, one pertaining to recreation, six concerning home adjustment and family status, 10 relating to work adjustment, and special space was provided at the end for additional comments. Three follow-up letters were sent at monthly intervals. The cover letter emphasizd the value to medical science of the patients' cooperation and assured them that their replies were confidential and to be used only for research and that they would remain anonymous. Of the total group of 83 questionnaires, 47 or 57% were returned completed. This compares with a return of 77.5% obtained by Jenkins with his group of paranoid schizophrenics. Jenkins explained the fact that his returns were above expectation largely on the basis of the likelihood that the paranoid patients were highly concerned that their cases be correctly evaluated. Of the experimental group of 45 patients, 62% completed the questionnaire, while 50% of the control group of 38 patients cooperated. This difference is not statistically significant. Of these returns, 60% were obtained from the first letter, 34% from the second letter, and 6% from the third.

Three judges, all of whom were experienced clinical psychologists with a Ph.D. and several years of clinical hospital experience, were given the questionnaires and

asked to rate them independently for improvement on a five-point scale as follows:

1. Much worse; frequently hospitalized since original hospitalization.
2. Worse; more incapacitated than before hospitalization; symptoms persist in exacerbated form; new symptoms have developed.
3. About the same; symptoms continue to interfere with work and/or social adjustment in about the same degree as before.
4. Improved, although occasional symptoms still present in some degree. Patient reports ability to work and/or to maintain adequate social adjustment.
5. No recurrence of psychiatric symptoms which required original hospitalization; patient reports satisfactory work and social adjustment.

The ratings of the three judges showed a high degree of consistency. All three agreed in 40% of th cases; one judge disagreed by one step in 51% of the cases; and in the remaining four cases there was no instance of a disagreement by more than two steps. The judgments of improvement for the two groups failed to show a statistically significant difference. Judges were basing their ratings on the answers to the questionnaire items as well as the patient's comments, which in many instances were extensive. In addition, there did not appear to be a significant relationship between judges' ratings and length of time since discharge.

Although the responses to the individual items are of interest, they seem to be of more importance when evaluated from qualitative analysis of individual records than treated solely as group frequencies. In order to make inferences from the results, one must keep in mind the possible importance of the differential effect of motivational factors in the replies of a group of veteran patients. Furthermore, generalizations may not be indicated on the basis of returns from only slightly more than half of the sample. The usefulness of this questionnaire type of follow-up has been doubted by some writers,[7] although, as noted above, with certain types of patients it has been fruitful. In the present study, the fact that the comparison is between a control and an experimental group makes some useful interpretations possible.

In the section on health and symptoms there were no significant differences on any of the items between the experimental and control groups. Of the total group, 75% of the experimental group and 84% of the control group stated that they had been helped by treatment, 7% of the experimental group and 16% of the control group responded negatively, and the remainder did not answer; 75% of the experimental group and 73% of the control group reported experiencing some recurrence of symptoms, although 89% of each group stated that they had not been rehospitalized, and only 32% of the experimental group and 26% of the control group reported that they had consulted a physician subsequent to hospitalization.

In the section concerning recreation, home and family items, there appears to be some difference suggesting better adjustment in the control group; 84% of the control group reported a reasonably successful adjustment as contrasted with 61% of the experimental group. Two possible contributing factors to explain this apparent difference are: 1. the experimental group were initially selected on the basis of being more difficult to treat with psychotherapy, and 2. the possibility, as suggested by other studies,[8] that the percentage of recovery in neurotic patients increases with the passage of time, which in this investigation would favor the control group.

Work adjustment is considered an important criterion of improvement in an objective evaluation of the post-discharge condition of psychiatric patients. There does not appear to be any significant difference between the two groups in this regard. In the carbon dioxide treated group, 72% reported holding the same or a better job, whereas in the control group 68% responded to this item similarly; 11% of the experimental group and 16% of the control group reported that they were not employed.

It is not feasible to make a direct comparison between the results of the present study and those quoted above from the literature for the reasons stated previously and because of the lack of uniformity in reporting the results of other studies as pointed out by Frank.[1] It seems safe to conclude, however, that in this follow-up study, as in our previous investigation which employed the Minnesota Multiphasic Personality Inventory profiles,[5] there is no apparent difference

in post-discharge adjustment between the group of patients treated with carbon dioxide inhalation therapy and concurrent psychotherapy, and the control group treated with psychotherapy alone. It should be noted that notwithstanding the lack of positive differences found in these investigations, carbon dioxide therapy remains in use as a method of treatment by our staff and is considered an important part of the treatment program. This is because of the clinical observation made by our psychiatrists, which is concurred in by others,[2] that some patients unable to talk about their feelings and to face their problems because of their defenses become more readily accessible to psychotherapy through the addition of carbon dioxide inhalations, and that similar beneficial results can be obtained with a more difficult group of patients. However, this clinical observation has not yet been investigated in a controlled study.

Summary

1. A follow-up study was conducted to cross-check by means of a questionnaire the results of a previous study of 45 patients who had received carbon dioxide inhalation therapy and concurrent psychotherapy, and a control group of 38 patients who were treated with psychotherapy alone. The carbon dioxide therapy group had a mean of 19.4 months and the control group had a mean of 43.5 months since discharge.

2. The returns were rated by three judges independently on a five-point scale. The judgments of improvement for the two groups failed to show a statistically significant difference.

3. The questionnaire results did not show significant differences between the two groups in the section on health and symptoms; 75% of the experimental group and 84% of the control group stated that they had been helped by treatment; 75% of the experimental group and 73% of the control group reported experiencing some recurrence of symptoms; 89% of each group stated that they had not been rehospitalized, 32% of the experimental group and 26% of the control group reported that they had consulted a physician subsequent to hospitalization. In the section containing recreation, home and family items, there appeared to be some difference suggesting better adjustment in the control group. Lastly, in the section evaluating work adjustment there did not appear to be any significant difference between the two groups.

4. A review and discussion of several previously published studies evaluating carbon dioxide inhalation therapy have been included.

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Modification of Electroshock Therapy by Succinylcholine Chloride

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Electroshock therapy has become well established as a treatment procedure in psychiatric practice. At Bournewood Hospital we have been using this method of treatment since 1944. Prior to the availability of succinylcholine chloride, we had given approximately 70,000 treatments.

Bournewood is one of the few private institutions of its type that make available to practicing psychiatrists the facilities for directly treating their own patients. We also have a full-time resident staff which closely follows, and, when necessary, supervises all therapeutic and diagnostic activities at the hospital. The authors are thus in the fortunate position of having intimate knowledge of, and, to a great extent of having participated in this large treatment program.

There is, of course, a certain amount of risk inherent in the treatment procedure. In our series, prior to the use of succinylcholine chloride, we have had five deaths immediately following electroshock therapy, or one death in 14,000 treatments.

Numerous investigators have reported various incidences of fractures resulting from treatment. Compressions of the vertebrae are the most frequent complication. Fractures of the humerus, femur, pelvis, and other bones also occur. We have had known compressions of the vertebrae in fewer than one per cent of total treatments. This type of compression requires no treatment and leads to no permanent disability. Fractures of the neck of the humerus, fractures of the pelvis, and fractures of the scapula have also occurred in our series.

It is also true that there have been patients who psychiatrically have been in desperate need of electroshock treatment, but this was not given because of a physical disability, such as severe heart disease.

Over this nine year period, we have been constantly looking for a method which would make electroshock therapy safer, without reducing the therapeutic effect. When treatment was first begun, the Cerletti-Bini type of current was tried. When the Glissando technique was introduced, we used that. In this technique, instead of the full current instantaneously applied, the current starts at zero and builds up to the full dose in 0.8 of a second, making the initial tonic spasm milder. When the Reiter machine and technique were introduced, we turned to that to get a "softer" convulsive seizure. However, we were still getting fractures in spite of these modifications. We were forced to conclude that the answer to our problem was not in electrical modification of the seizure.

We used curare as a muscle relaxant, but abandoned it after a short period of time, since this introduced additional risk to life. Curare is too slow acting. Its effect is too prolonged. There is danger of delayed reaction, in the dosage necessary for complete muscle relaxation. It never was used routinely. It was tried on patients who were severely ill psychiatrically but in whom there was contraindication to convulsive therapy. The risks of treating were carefully weighed against the risks of not treating. Soon, however, we discouraged the use of curare even in these cases.

In the last three years there has been introduced a modification of electroshock therapy which removes practically all of the previous risks inherent in the treatment. This involves the use of succinylcholine chloride (Anectine*) to modify the convulsive seizure. Succinylcholine chloride is a rapid, short acting skeletal muscle relaxant, acting at the myoneural junction. The following paper will present our experiences with this drug.

When succinylcholine chloride was introduced, we recognized its advantages. Two years ago we began using this drug with

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thiopental sodium (Pentothal sodium) in poor risk cases. With the safety and effectiveness of this method repeatedly demonstrated, we began to use it more frequently, until, at present, about 90 per cent of our patients are being treated by this procedure. We have given 7,500 treatments by this method, 6,000 in the last year.

At the onset, anesthesiologists were called to administer the thiopental sodium, succinylcholine chloride and oxygen. The staff here at Bournewood, after they had become skilled in the necessary procedures, began giving the treatments without anesthesiologists. Eight months ago, a full time nurse anesthetist was employed by the hospital. She is present in the treatment room six mornings a week to carry out the necessary procedures. Since then, succinylcholine chloride treatments have been used more frequently by our visiting psychiatrists.

Some authorities say that the procedure should not be carried out except by a qualified anesthetist. We would like to modify this statement by saying that the procedure can be carried out by qualified physicians and nurse anesthetists, who are skilled in the technique of giving oxygen under positive pressure, and who are capable of inserting an endotracheal catheter.

The following is our technique:

The patient has no food for four hours. In our practice, treatments are given in the mornings, and breakfast is omitted. Atropine sulfate, gr 1/75 (0.8 mgm) is given routinely intramuscularly one-half hour before treatment. To save time in treating out-patients, the atropine can be given intravenously a few minutes before the treatment. The patient lies on a high bed with a slender pillow under the head. No hyperextension of the spine is necessary. If the patient is edentulous, no mouth gag is necessary. A felt gag is inserted just prior to the electric shock to protect the teeth. This is important as the jaw will contract forcefully, due to direct application of the current to the muscles.

The oxygen equipment consists of a tank yoke adapter, with reducing valve and flow meter mounted on an E size tank and tank carrier. A Heidbrink inhaler casting No. 41, five liter bag and anatomical face mask complete the unit. A six foot length of one-half inch rubber tubing connects the inhaler to the reducing valve. A surgical cart on wheels holds the equipment needed to assist in maintaining a patent airway for every patient and in meeting any emergency arising from anesthesia. The Guedel-type oral airway is the one we use. Other aids include the nasal airway, oral and nasal endotracheal catheters, and laryngoscope. A supply of emergency drugs is also on hand including atropine, ephedrine, mephenteramine, epinephrine, met-amphetamine and one percent procaine.

Thiopental sodium in 5 per cent solution is prepared daily. To the commercially prepared isotonic salt solution 300 cc size bottle, 15 grams of thiopental sodium is added. For ease in administration a short length of intravenous tubing, with a needle adapter at one end, is attached to a 10 cc metal tip syringe. The syringes with tubing attached are filled prior to the treatment schedule in sufficient quantity to meet the day's need. A like quantity of 5 cc syringes are filled with 2 or 3 cc of succinylcholine chloride.

The thiopental sodium is administered very slowly until the patient fails to respond to mild external stimuli. Then the succinylcholine chloride is given by inserting the needle through the rubber intravenous tubing close to the needle adapter. The tubing is pinched tightly to prevent any back flow. An additional centimeter of thiopental sodium follows the succinylcholine chloride to flush the adapter and needle. The succinylcholine chloride is given rapidly, causing in most patients slight muscular twitchings. Cessation of the twitching and apnea are the clinical signs of maximum succinylcholine chloride effect. The usual time is 60 seconds, but this varies from 40 to 120 seconds. As the patient's normal respiratory effort decreases, his respiration is assisted by light manual pressure on the breathing bag. During the period of apnea following the succinylcholine chloride injection, the patient is well oxygenated at all times. Normal respiration is usually restored in three to five minutes. Prostigmine is not an antidote and is not to be used. Care is exercised to maintain a patent airway. Usually a Guedel type airway is adequate. As soon as the normal respiratory movements are resumed, the oxygen is discontinued and the patient is turned on his side for the recovery period. Most patients will respond to stimuli in fifteen or twenty minutes although if not disturbed they will sleep for longer.

Each patient receives 250 to 300 milligrams of thiopental sodium. Occasionally a muscular young male will require as much as 500 milligrams. Rarely do we exceed this. In starting a series of treatments, the initial dose of succinylcholine chloride is estimated according to age, size, and physical status of the patient. Most patients do well on 50 milligrams of succinylcholine chloride. A strong muscular male may require as much as 80. Slight and aged patients sometimes receive as little as 20 milligrams. Since our prime purpose is to eliminate the risk of fractures and to administer a non-traumatic treatment to poor risk patients, we do not worry about giving more succinylcholine chloride than necessary. We prefer to give more rather than too little. Other workers use smaller amounts, modifying the convulsion, but we prefer full protection.

Since more current is necessary when thiopental

sodium is used, the maximum or close-to-maximum current is administered. When the current is administered, there will be spasm of the jaw, and slight movement of the arms and legs, followed by a slight twitching of the toes, fingers, and face to show that a convulsive dose has been given. The amount of muscle paralysis varies with the patient, and varies directly with the amount of succinylcholine chloride used.

In our practice, we have an attendant gently hold the shoulders, especially during the first treatment, in case the dose of succinylcholine chloride given does not sufficiently protect the patient from a convulsive seizure. Care should be exercised to see that the thiopental sodium and/or succinylcholine chloride should not be given extravascularly. If the patient is sufficiently anesthetized, and there is some indication that the succinylcholine chloride has not been effective, we feel that it is advisable to give another injection intravenously and wait an additional sixty seconds to avoid the possibility of a generalized convulsion. In the rare case where there has been some extravascular injection, no immediate or delayed succinylcholine chloride effect was noticed, and no local complications were encountered.

Other workers in this field have used slightly different techniques in administering the thiopental sodium and succinylcholine chloride. Montagu[1] and Holt[2] mix the thiopental sodium and succinylcholine chloride in the same syringe, and inject immediately. This has to be done at once as the succinylcholine chloride precipitates the thiopental sodium and the alkaline solution destroys the succinylcholine chloride. Another objection to this method is that the dose of thiopental sodium has to be evaluated prior to injection and cannot be varied with the needs of the patient.

Alexander[3] advocated administering 0.4 per cent thiopental sodium solution by intravenous drip, and, when the desired level of anesthesia is reached, injecting the succinylcholine chloride through the tubing. There is no objection to this, except that it is time consuming. We do not feel there is sufficient advantage to warrant its use.

Murray[4] uses the succinylcholine chloride without any preliminary barbiturate. In our experience with this method, we encountered considerable resistance from the patients, since they remember the period of apnea as a very uncomfortable feeling. "I felt as if I were buried alive. I was awake, knew what was going on, but couldn't move or breathe." The patients find our method of treatment pleasant, and we have encountered no resistance.

The main difficulty in the treatment is that the veins may be poor or may become sclerosed. It may, therefore, become difficult to give intravenous medication. On the theory that a 5 per cent solution of thiopental sodium may be causing some sclerosis, we have recently started using a 3 per cent solution and find this satisfactory. Only in one or two cases have we had to stop the use of succinylcholine chloride because of difficulty with veins.

Seventy-five hundred treatments have been given. Patients with recent fractures, severe hypertension, previous cerebrovascular accidents, previous coronary thrombosis, anginal syndrome, cardiac arrhythmias, and even two patients six months after cardiac surgery have been treated. There have been no medical complications and no complaints of muscle pain or fractures. Only on one occasion has it been necessary to introduce an endotracheal catheter, and this was because of mechanical difficulty and not laryngeal spasm. One patient vomited, was immediately placed on her side, and no complications ensued. One patient had some difficulty because of increased salivation and mucus, not adequately controlled by atropine. One patient developed Cheyne-Stokes type of respiration following treatment, but made an uneventful recovery.

Liver disease and severe anemia are felt to be relative contraindications since, in these conditions, there is a deficiency in cholinesterase, the substance which destroys the succinylcholine chloride. There may, therefore, be a prolonged period before respiration is restored. Our longest period has been twenty minutes. When this complication is encountered, it is not serious, as oxygen under pressure can be continued, and the patient does not become cyanotic.

Our consultant internists have recommended the following procedures, and we have found them very useful. If extrasystoles are present, we give 5 gr (0.3 grams) of quinidine by mouth one and one-half hours before the treatment. Should extrasystoles develop following the first treatment, the same procedure is carried out. If

anginal syndrome is present, we give gr 1/150 (0.4 mgm) of nitroglycerine under the tongue five minutes before treatment. Asthmatic patients are given aminophyllin 3-3/4 gr (225 mgm) intramuscularly one-half hour before the treatment to prevent an acute asthmatic episode. We have given thiopental sodium and succinylcholine chloride to patients who are on chlorpromazine medication with no complications or difficulty.

Experience with 7,500 treatments has shown us that treatment with succinylcholine chloride is safer than unmodified electro-convulsive therapy. Poor risk patients can be treated and no complications have been encountered. The patient is well oxygenated throughout, and no cyanosis occurs, as it does with standard type of convulsive treatment. The pulse remains slow and regular. There is a rise in blood pressure, but not as high as with standard treatment. Once normal respiration is restored, there is no danger of cessation of respiration due to delayed effect, as there is with curare. However, it is essential that the individual using the treatment be skilled in the administration of oxygen under positive pressure, and in the technique of maintaining an adequate airway for respiratory exchange.

Summary

1. The standard type of convulsive electroshock therapy has inherent risks. In our series of 70,000 treatments without succinylcholine chloride there have been five deaths and fewer than one per cent of fractures. Most of these fractures are compressions of the vertebrae, which require no treatment.

2. Modification of electro-convulsive therapy with thiopental sodium and succinylcholine chloride is a much safer treatment as shown by the absence of fractures and medical complications in our series of 7,500 treatments.

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Neurological and Neuropathological Conference

HAMILTON FORD, M.D., and K. M. EARLE, M.D., *Editors*

Case No. PM 9527

Presentation

This 24-year-old white male was admitted to the Neurosurgical Service at John Sealy Hospital on January 3, 1954, and expired on January 12, 1954.

He had apparently been well up until Thanksgiving Day of 1953 when he complained of a sudden, severe frontal headache with some neck pain and stiffness and vomiting. He was hospitalized elsewhere for a period of about 3 days and these symptoms subsided. He had another similar episode for which he was hospitalized in another city. Here no diagnosis was made and the symptoms disappeared. His last siege of headaches occurred the latter part of December, 1953, when he became lethargic and disoriented and remained so. Between bouts of headache the patient was well enough to return to work. The headaches had not been localized to one side or the other and there had been no relevant past history concerning headaches, eye, ear, nose or throat symptoms, nor was there associated weakness of any part of the body with these episodes. There was no history of trauma. A lumbar puncture was done at St. Mary's Infirmary was reported to reveal bloody fluid.

The patient was transferred to the Neurosurgical Service at John Sealy Hospital. On admission he was a well developed white male who was somnolent but would arouse on stimulation, neck was stiff, and no bruit was heard on the skull. Neurological examination revealed a drowsy and disoriented individual. There was no evidence of any retinal hemorrhages or edema, and no extra-ocular palsies. The face moved symmetrically, and there was no evidence of any weakness of the extremities. Reflexes were depressed throughout, there were no pathological reflexes, and the remaining examination was within normal limits.

The following day a percutaneous carotid arteriogram was done on the left side. Following this the

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patient gradually improved to the point where he was rather alert and was eating quite well. There were no neurological findings. He was still somewhat disoriented but this was becoming less apparent each day. On 1/9/54 a lumbar puncture revealed an initial pressure of 220 mm. of water with a reddish-brown color.

His arterial blood pressure was 180/120 with a pulse of 100, respirations 24, and temperature 102.6°. Hourly blood pressure readings remained at a level of 160 to 180 systolic and 90 to 110 diastolic for the next 2 days, except while under anesthesia, when it came down to normal range. As time went on, his blood pressure dropped somewhat but still ranged around 150 to 160 systolic and 90 to 100 diastolic. Temperature also came down to normal within the next day. X-rays of the skull and chest taken at another hospital, but reviewed here, were considered normal. Peripheral blood studies and urine were non-contributory.

Suddenly at 2 A.M. on January 12th, the patient had a sudden severe headache and became comatose while an attendant was taking his blood pressure. It immediately rose to 180/140, and respirations dropped to 6 to 10 per minute. Lumbar puncture revealed an initial pressure of 380 mm. of water with a closing pressure of 240 mm. and appeared grossly bloody. The patient progressively went downhill and expired 3 hours after this last onset.

Clinical Discussion

Dr. Ira Jackson:

The diagnosis here is a rather obvious one, namely that of spontaneous subarachnoid hemorrhage. The first attack of bleeding occurred on Thanksgiving Day and this presented itself with headache and some neck pain and stiffness. The latter is due to blood in the cervical subarachnoid space causing meningeal irritation. About five years ago, I presented the experimental material showing that the fever and meningeal signs occur from the breakdown products of blood in the subarachnoid space and that the most responsible factor is probably from the heme component of the blood. The other factors or components of blood are relatively non-toxic. This coincides with most episodes of subarachnoid bleeding (Archives of Neurology and Psychiatry, Vol. 42, 1949). The patient apparently had a rather marked episode in December which caused him to be brought to Galveston. The absence of any focal neurological findings is not unusual and would make you think more of a saccular aneurysm around the circle of Willis. This also would make you think that there probably was not an intracerebral hematoma although there could well be one in the frontal lobes.

The causes of spontaneous subarachnoid hemorrhage are many, but probably 90% are caused by saccular aneurysms. The remaining 10% are of multiple etiology, as arteriovenous aneurysms, blood dyscrasias, brain tumors, essential hypertension, and arteriosclerosis. Epileptic seizures present in about 50% of patients with arteriovenous aneurysms are mainly focal in character, and spontaneous subarachnoid hemorrhage occurs in 20%. Only about 1% have brain tumors and it is usually in these cases in which the neoplasm suddenly hemorrhages. Such patients may have had symptoms before, or this may be their initial symptom. The greatest confusion in differential diagnosis is in the patient with essential hypertension. For some time it was thought that if a patient had increased arterial pressure and an attack of unconsciousness with bloody fluid, that the sole cause was the hypertension. However, this is not so. About 18 to 20% of patients with ruptured intracranial aneurysms also have hypertension. Therefore a patient may have both diseases and should be so considered until proven otherwise. Any patient who presents a story of a sudden onset of severe headache with neck pain should be considered as having a possible intracranial aneurysm. This even more so, if there is associated sudden unconsciousness. A lumbar puncture will most often disclose the bleeding. However, if there is no blood in the spinal fluid, this does not rule out diagnosis of intracranial aneurysm. I remember a young woman in her early thirties who had sudden severe headache with no other findings. Her family physician did a lumbar puncture and the spinal fluid was clear and colorless. However, in spite of this, he felt that she had such a lesion and referred her to me for an arteriogram. Our findings were totally negative but at his insistence we did an arteriogram and found an aneurysm of the anterior communicating artery. This was certainly to my surprise. I merely point this out to show that blood in the spinal fluid is not the sole answer.

Localization of the aneurysm is oftentimes made easier because of more pro-

nounced findings as hemiplegia, extraocular palsies, etc. The most frequent cause of an isolated third nerve palsy is intracranial aneurysm, most commonly of the internal carotid artery. However, aneurysms following rupture frequently do not give any focal signs. Occasionally, shortly after the rupture, there may be some findings present such as a Babinski and an alteration of the deep tendon reflexes, and this will give the surgeon a clue as to which side to do the arteriogram on.

The introduction of 35% diodrast into the carotid artery is performed after the patient's general condition is satisfactory. In our case an aneurysm of the anterior communicating artery was found. Treatment of such aneurysms is somewhat variable from clinic to clinic and from surgeon to surgeon and also varies from time to time with the same surgeons. For many years, there was no surgical treatment and then followed an era of carotid ligation. Following this, an intracranial attack was made on such aneurysms and these results somewhat varied. Professor Olivecrona from Sweden has a remarkable series with no mortalities. However, none of his patients were operated upon during the acute stage and not until three or four weeks after the initial onset. On the other hand, Hamby in Buffalo reports that nine out of 11 succumbed following surgery. There are many factors involved here. One is that some of these are associated with intracerebral hematomas and the other is, that if operated upon early, there is considerable cerebral edema associated with it making the surgery very difficult. The results of Olivecrona are based on the fact that he waited until his patients were symptoms-free before operating, therefore making an elective procedure out of it. Hence many of the patients with spontaneous subarachnoid hemorrhage died before reaching surgery in that clinic.

There has recently been more enthusiasm for carotid ligation for aneurysm about the circle of Willis. One of the chief objections to this procedure had been that ligation in the neck was not going to alter the aneurysm intracranially unless severe neurological signs ensued. However, there has been recently some very authentic experimental work on humans, showing that carotid ligation does diminish the intraarterial pressure over the cortex, on the same side, and frequently on the opposite side. For this reason the vogue of carotid ligation has returned. The main advantage of ligation is that the morbidity is considerably less than that of the intracranial procedure. We have done some intracranial attacks here on aneurysms of the anterior communicating artery with surgical success. However, the morbidity has been of some concern. These patients have done well as far as life and death are concerned but do not, as a rule, have the intellectual capacity for gainful employment that they previously had. This deficit however, may not necessarily be due to the surgical procedure but may well have been due to the initial rupture and brain damage at that time. This point was well brought home last year when Dr. Snodgrass, Sir Geoffrey Jefferson of Manchester, England and myself discussed this problem. Sir Geoffrey spoke about a young college student from Scotland, whom he had recently operated on for such an aneurysm. This patient is doing well but does not have the intellectual ability to return to college. Sir Geoffrey felt that the patient would have been better off had he not been operated on. I think, this in itself, deserves some thought. One then turns to conservative therapy which may briefly be mentioned. The results here are mostly presented by the Toronto group showing that patients who survive three months after their initial rupture have a moderately good chance of survival, while the patient who has his first rupture has a relatively high chance of having a second rupture in two weeks, and the mortality increases progressively. Fifty per cent of all patients with subarachnoid hemorrhage admitted to the hospital succumb following their first rupture while this diminishes with each successful rupture. Nevertheless, the most frequent period of second rupture is between the second and third week following the first rupture.

The problem shown here is that this patient showed recovery following four ruptures before the fifth attack caused death. Apparently, after each attack the patient had recovered to almost normal level and there-

fore made it rather difficult to become aggressive with a somewhat precarious procedure. Nevertheless, having seen many such patients, who have had second or third ruptures while having a perfectly normal interval, has made the neurosurgeon somewhat aggressive toward the problem of intracranial aneurysm. It would seem that at present the trend in some clinics is toward internal carotid artery ligation within a week after rupture. The arteriogram, of course, is done as soon as the patient's general condition permits this procedure.

Pathological Diagnoses:

1. Aneurysm of anterior communicating artery with rupture into right frontal lobe.
2. Intracerebral, intraventricular and subarachnoid hemorrhage due to ruptured aneurysm.

Pathological Findings:

Permission for necropsy was limited to the head only.

The brain weighs 1,420 grams. The right cerebral hemisphere is larger than the left. The subarachnoid space at the base of the brain is filled with recent hemorrhage. The inferior surface of the right frontal lobe is lacerated and fresh hemorrhage is visible within the frontal centrum.

When blood and parts of the orbital gyri are removed, a large aneurysm is visible arising from the anterior communicating artery at the anastomosis with the right anterior cerebral artery. This aneurysm is ruptured and part of its wall is torn away by the hemorrhage. The sac that remains indicates that the intact aneurysm measured about 1 cm. in diameter.

The hemorrhage resulting from this ruptured aneurysm has dissected into the right frontal centrum ovale and ruptured into the right lateral ventricle. The anterior part of the corpus callosum has been destroyed. The entire ventricular system is filled with blood and the basal cisterns and subarachnoid space of the inferior surface of the cerebellum contains recent hemorrhage. The subarachnoid spread has not apparently had time to extend over the entire surface of the brain. In small areas over the convexities of the cerebral hemispheres, there is brown discoloration indicative of staining by previous, old subarachnoid hemorrhage.

Histological sections reveal recent and old subarachnoid hemorrhage with the large area of intracerebral hemorrhage described above. The aneurysm is fragmented by rupture, but shows no sign of inflammation. The vessels show very slight arteriosclerotic changes. Petechial hemorrhages are present in the anterior hypothalamus. The neurones and glial elements show acute non-specific changes.

Comment:

This aneurysm has the features of a congenital aneurysm arising from the anterior communicating artery at the anastomosis with the right anterior cerebral artery. These aneurysms are considered to be the result of a congenital defect in the elastica of the vessel wall. These aneurysms are seldom seen in children, but are found frequently in adults. Often they are incidental findings. The aneurysms apparently grow progressively larger by slow expansion of the congenital defect in the wall.

This is one of the commonest locations for these aneurysms and is a dangerous location because the small vessels of the Circle of Willis which supply the anterior hypothalamus are located just behind this region. Although this region is accessible to surgery, ligation of aneurysms of this location frequently results in damage to vessels supplying the hypothalamus with subsequent softening and death.

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